In the outstanding Office Action, claims 1-11 and 13 were rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 4,377,572 to Schwarz et al. ("Schwarz") in view of WO 92/13495 to Tripodi ("Tripodi"). Applicants respectfully assert that the present claims and remarks obviate this rejection.

Applicants' rejected claims are directed to therapeutic compositions of high fibrinogen yield and therapeutically effective strength. For example, independent claim 1 specifies that about 95%, or greater, of the total protein present in the composition is fibrinogen, and independent claim 2 specifies that the composition contains less than about 30% of proteins other than fibrinogen. Similarly, independent claim 13 is directed to a reactive therapeutic composition of thrombin and fibrinogen composition. This claim also specifies that about 95%, or greater, of the total protein present in the fibrinogen composition is fibrinogen.

The above claims further specify, in part, that the clottable fibrinogen is obtained from precipitating fibrinogen from a sample of non-human mammalian blood plasma with polyethylene glycol 1000 and reprecipitating the fibrinogen with glycine, wherein precipitation of the fibrinogen with polyethylene glycol is performed only once, such that at least about 90% of the fibrinogen present in the sample is recovered. *See* page 26 of Applicants' specification.

As disclosed in Applicants' specification at page 27, precipitation of fibrinogen with PEG 1000 leads to a cohesive fibrinogen precipitate that is more readily collected, for resuspension, than fibrinogen precipitate resulting from contact with, for example, PEG 8000. Accordingly, use of low molecular weight PEG (such as PEG 1000) facilitates recovery of clottable fibrinogen.

Referring now to the Schwarz reference cited by the Examiner, Applicants maintain that this reference does not disclose nor suggest the presently claimed invention. For example, the tissue adhesive of Schwarz includes fibrinogen in an amount of at least 70 mg/ml (Col. 1, lines 57-61), as recognized by the Examiner. As distinguished in Applicants' specification at page 4, line 21 continuing to page 5, line 19:

> [t]herapeutic adhesive fibrinogen compositions disclosed [in Schwarz] are stated to require concentrations of fibrinogen of at least about 70 mg/ml (which may again be diluted 1:1 at the treatment site by contact with a thrombin-containing solution).
>
> The present invention relates to fibrinogen-containing compositions that have *surprising clinical (medical) utility* as adhesives, sealants, or hemostatic agents, and that provide therapeutically effective strength at fibrinogen concentrations at the treatment site of, for example, *only about 10 mg/ml. The more dilute and less viscous nature of the therapeutic compositions provided according to the practice of the present invention decreases substantially the time necessary to resuspend such compositions from the lyophilized form, an important advantage in, for example, the hospital emergency room. Filtration of the fibrinogen during processing is also facilitated.*

Thus, the tissue adhesive of Schwarz appears to even teach away from the present invention. Moreover, as further disclosed in Applicants' specification at page 14, lines 9-20:

> [t]he use of numerous fibrinogen-containing compositions known in the art has been stated to require the presence therein of a minimum of about 70 mg/ml of fibrinogen, there being derived therefrom, fibrinogen, of at least 35 mg/ml, at the treatment site. The fibrinogen-containing therapeutic compositions of the present invention are effective, however, even when the final concentration of fibrinogen derived therefrom at the treatment site (taking into account the volume of any thrombin solution applied therewith) is only about 10 mg/ml or lower.

In the outstanding Action at page 4, the Examiner recognizes that the instant invention provides, in part, "that the therapeutically effective strength at fibrinogen concentration is only about 10 mg/ml." Applicants respectfully point out that independent claim 1 has been further clarified, as suggested by the Examiner, to recite "wherein said therapeutically effective fibrinogen concentration at said site is about 10 mg/ml or less." Similarly, independent claims 2 and 13 have been clarified to recite "wherein said therapeutically effective fibrinogen concentration at said site is about 30 mg/ml or less." Moreover, new dependent claim 38 specifies that the therapeutically effective fibrinogen concentration at the site advantageously is about 10 mg/ml. Similarly, new dependent claims 39 and 40 specify that the therapeutically effective fibrinogen concentration at the site advantageously is about 30 mg/ml. New dependent claim 41 further specifies that the therapeutically effective fibrinogen concentration at the site is between about 5 mg/ml to about 10 mg/ml. Accordingly, it is respectfully asserted that Schwartz does not disclose nor even suggest Applicants' claimed invention.

Applicants further respectfully assert that the addition of Tripodi does not cure the shortcomings of Schwartz. Tripodi is directed to a fibrinogen based adhesive.

However, in contrast to Applicants' claimed invention, Tripodi recommends the use of PEG-8000 (Page 6). As disclosed in Applicants' specification at page 27, precipitation of fibrinogen with PEG 1000 leads to a cohesive fibrinogen precipitate that is more readily collected, for resuspension, than fibrinogen precipitate resulting from contact with, for example, PEG 8000. Accordingly, use of low molecular weight PEG (such as PEG 1000) facilitates recovery of clottable fibrinogen. Such clottable fibrinogen is set forth in the present claims.

In view of the foregoing, reconsideration and withdrawal of this rejection is respectfully requested.

Claims 1-3, 7-11 and 13-14 were then rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 4,427,650 to Stroetmann ("Stroetmann '650") or U.S. Patent No. 4,442,655 to Stroetmann ("Stroetmann '655") in view of Tripodi. Similarly, Claims 1-3, 5, 7-11 and 13-14 were rejected under 35 U.S.C. § 103(a) as being obvious over Stroetmann '650 or Stroetmann '655 in view of Tripodi and further in view of the article, entitled, *The Measurement of Fibrinogen and its Derivatives* by Farrell et al. ("Farrell"). Applicants respectfully traverse these rejections.

The Examiner contends at page 3 of the outstanding Action that the foregoing rejections are "for the reasons set forth in the previous office action ..." Applicants respectfully point out that no such rejections were issued in the previous Action

of April 10, 2002. Accordingly, the Patent Office has not met its burden of establishing a *prima facie* case of obviousness.

Moreover, in contrast to the subject matter of the rejected claims, Stroetmann '650 is directed to enriched plasma derivative for advancement of wound closure and healing, wherein the fibrinogen is isolated from *human plasma* (Col. 3, line 17, emphasis added). Specifically, Stroetmann '650 discloses that "it has been recognized according to the invention that the fibrinogen isolated from human plasma shall largely be free from cryo-insoluble globulin . . ." (Col. 3, lines 15-31).

However, as recited in the afore-referenced claims, the fibrinogen is obtained from non-human mammals. As further described in Applicants' specification at page 10, line 15 continuing to page 12, line 10 (emphasis added):

> [t]he therapeutic compositions of the invention comprise non-autologous, non-single donor mammalian fibrinogen . . . Preferred donors are mammals other than the human . . . Fibrinogen compositions that could be provided from mammalian species other than the human are disclosed, for example, in U.S. Patents No. 4,377,572 and 4,362,567. However, the therapeutic compositions defined therein *are stated to contain at least about 70 mg/ml or more of fibrinogen (prior to any dilution at the site of treatment) leading potentially to the presence also therein of a substantial amount of additional and antigenic protein impurities*, there resulting an associated risk of severe immune response. . .

Thus, Stroetmann '650 also appears to teach away from the presently claimed invention, as does Stroetmann '655. That is, Stroetmann '655 discloses that "[p]referably, a relatively high fibrinogen concentration of approx. 50-80 mg/ml is provided . . . Therefore, an

increased fibrinogen concentration in the initial solution leads to a denser end product of higher mechanical strength" (Col. 4, lines 14-21).

It is further respectfully asserted that the addition of Tripodi or Farrell does not cure the shortcomings of either Stroetmann '650 or '655. Tripodi was described above and, for the foregoing reasons, it is respectfully asserted that this reference does not cure the shortcomings of either Stroetmann '650 or '655.

Farrell is a technical paper merely documenting the investigation of the minimal concentration of ε-amino caproic acid in plasma required to induce total suppression of *in vitro* fibrinogenolysis and fibrinolysis, as well as the effect this EACA concentration produced on recovery of thrombin clottable fibrinogen estimates. These results were compared with clot recovery from plasma to which either fibrin degradation products or fibrinogen degradation products had been added (*See*, page 328 of Farrell).

In view of the foregoing, it is respectfully asserted that there is no teaching, suggestion or motivation in either Stroetmann '650, Stroetmann '655, Farrell or Tripodi that would lead one of ordinary skill in the art to combine and modify these references, and the Examiner has pointed to no such suggestion. Accordingly, in view of the foregoing amendments and remarks, withdrawal of these rejections is believed to be warranted.

Lastly, independent claim 2 and claim 12 depending therefrom were rejected under 35 U.S.C. § 103(a) as being obvious over Stroetmann '655 in view of the abstract of *Preparation of Rat Fibrinogen* by Richter et al. ("Richter") and Tripodi.

Tripodi and Stroetmann '655 have been described above. Applicants respectfully assert that the addition of Richter does not disclose nor suggest the presently claimed invention. For example, Richter merely is directed to the preparation of rat fibrinogen and a comparison of the intermediate, as well as final products, of rat fibrinogen with those of human fibrinogen (Abstract). Accordingly, this rejection also should be reconsidered and withdrawn.

In furtherance to the above remarks directed to claims 1-14, which were rejected in the outstanding Action, Applicants respectfully point out that Group I, claims 1-14, **26 and 35-37** were previously elected by Applicants for prosecution. Applicants respectfully direct the Examiner's attention to these claims and also note that Claim 26 has been canceled by the subject Amendment.

It is respectfully submitted that the subject application is in condition for allowance. A Notice of Allowance is respectfully requested.

The Examiner is invited to telephone the undersigned attorney at 212-425-7200 if it is believed that a discussion would advance the prosecution of this application.

Authorization is also hereby given to charge any deficiency in fees in connection with this Amendment to our Deposit Account No. 11-0600.

Also, attached hereto is a Marked-up Version Showing Changes Made By The Present Amendment in accordance with 37 C.F.R. § 1.121.

Respectfully submitted,

Date: June 9, 2003

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Marked-up Version Showing Changes Made
By The Present Amendment (37 C.F.R. § 1.121)

In the Claims:

Please amend claims 1-2 and 13, cancel claim 26 and add new claims 38-41 as follows:

1. (Amended) A therapeutic composition effective on contact with thrombin at a site of treatment in a patient as a tissue adhesive, hemostat or sealant, said composition comprising non-autologous, non-single donor mammalian, clottable fibrinogen recovered from a process comprising precipitating fibrinogen from a sample of non-human, mammalian blood plasma with polyethylene glycol 1000 and reprecipitating said fibrinogen with glycine, wherein precipitation of said fibrinogen with polyethylene glycol is performed only once, such that at least about 90% of the fibrinogen present in said sample is recovered, wherein said recovered fibrinogen polymerizes when provided in solution at said site at a therapeutically effective fibrinogen concentration of about 10 mg/ml thereof or less, to a fibrin network having therapeutically effective strength, wherein said therapeutically effective fibrinogen concentration at said site is about 10 mg/ml or less, and said composition further comprising a sufficient amount of one or more physiologically-compatible solutes such that said composition, if formulated as a lyophilized material, can be reconstituted therefrom at room temperature in sterile water for injection in about 30 minutes or less, at about 25

mg/ml of said fibrinogen; wherein about 95%, or greater, of total protein present in said composition is fibrinogen.

2. (Amended) A therapeutic composition effective on contact with thrombin at a site of treatment in a patient as a tissue adhesive, hemostat or sealant, said composition comprising non-autologous, non-single donor mammalian, clottable fibrinogen recovered from a process comprising precipitating fibrinogen from a sample of non-human, mammalian blood plasma with polyethylene glycol 1000 and reprecipitating said fibrinogen with glycine, wherein precipitation of said fibrinogen with polyethylene glycol is performed only once, such that at least about 90% of the fibrinogen present in said sample is recovered, wherein said recovered fibrinogen polymerizes when provided in solution at said site at a therapeutically effective fibrinogen concentration of about 30 mg/ml thereof or less, to a fibrin network having therapeutically effective strength,

wherein said therapeutically effective fibrinogen concentration at said site is about 30 mg/ml or less,

wherein said composition contains less than about 30% (w/w), based on total protein mass present therein, of proteins other than fibrinogen, and said composition further comprises a sufficient amount of one or more low molecular weight physiologically-compatible solutes such that said composition, if formulated as a lyophilized material, can be reconstituted therefrom at room temperature in sterile water for injection in about 30 minutes or less, at about 25 mg/ml of said fibrinogen.

13. (Amended) A reactive therapeutic composition effective on contact at a site of treatment in a patient as a tissue adhesive, hemostat or sealant, said composition comprising, per milliliter thereof, between about 0.05 and about 500 NIH units of thrombin and also, per milliliter, between about 5 and about 30 mg of a fibrinogen composition wherein clottable fibrinogen is recovered from a process comprising precipitating fibrinogen from a sample of non-human, mammalian blood plasma with polyethylene glycol 1000 and reprecipitating said fibrinogen with glycine, wherein precipitation of said fibrinogen with polyethylene glycol is performed only once, such that at least about 90% of the fibrinogen present in said sample is recovered, said recovered fibrinogen polymerizes to a fibrin network having therapeutically effective strength, when present at said site at a therapeutically effective fibrinogen concentration of about 30 mg/ml or less, wherein said therapeutically effective fibrinogen concentration at said site is about 30 mg/ml or less; wherein about 95%, or greater, of total protein present in said fibrinogen composition is fibrinogen.

Cancel Claim 26.

38. (New) The composition of Claim 1 wherein said therapeutically effective fibrinogen concentration at said site is about 10 mg/ml.

39. (New) The composition of Claim 2 wherein said therapeutically effective fibrinogen concentration at said site is about 30 mg/ml.

40. (New) The composition of Claim 13 wherein said therapeutically effective fibrinogen concentration at said site is about 30 mg/ml.

41. (New) The composition of Claim 1 wherein said therapeutically effective fibrinogen concentration at said site is between about 5 mg/ml to about 10 mg/ml.